UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,661	12/15/2003	Avner Yayon	81408-4400	5324

28765 7590 07/25/2007
WINSTON & STRAWN LLP
PATENT DEPARTMENT
1700 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,661	YAYON ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-15 and 17-49* is/are pending in the application.

4a) Of the above claim(s) *11-14,18-21,23-30 and 32-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,15,17,22 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2003 and 20 April 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/2003 and 6/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

1. The amendment filed December 4, 2006 is acknowledged and has been entered. Claims 1, 4-8, 10, 15, 17, 32 and 38 have been amended. Claims 2-3 and 16 have been cancelled. Claims 48-49 are newly added.

2. The amendment filed April 20, 2007 is acknowledged and has been entered. Claims 7, 11-12, 18, 23 and 25 have been amended.

3. The election with traverse filed December 4, 2006, is acknowledged and has been entered.

Applicants has elected to prosecute the invention of the Group XVI, claims 4-10, 15-22, and 31, drawn to a molecule comprising the antigen-binding portion of an isolated antibody comprising a V_H region of SEQ ID NO: 113 and V_L region of SEQ ID NO: 102 or a V_H–CDR3 region of SEQ ID NO: 24 and V_L–CDR3 region of SEQ ID NO: 25, which has an increased affinity for FGFR3 and which block constitutive activation of said FGFR3.

Claim 1 is a linking claim and has been examined with claims directed to the elected invention.

Notably, Applicant has corrected a sequence compliance problem (see action mailed 1/12/2007); so for clarity the elected invention, as now claimed, is a molecule comprising an antigen binding portion of an isolated antibody that comprises a V_H region of SEQ ID NO: 106 and V_L region of SEQ ID NO: 95 (see claim amendment filed April 20, 2007).

4. Claims 1, 4-15, and 17-49 are pending. Claims 11-14, 18-21, 23-30, 32-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 4, 2006.

Notably, claims 18-21 and 48-49 have been withdrawn as they are drawn to non-elected subject matter.

5. Claims 1, 4-10, 15, 17, 22 and 31 are under examination.

Election/Restrictions

6. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed October 5, 2006, is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

The traversal is on the following grounds: "RPTKs are unified by several features, including an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase domain. The RPTKs are further activated by dimerization and ligand binding to the dimerized form. In fact, the structure and function of RPTKs are highly conserved throughout evolution from nematodes (C. elegans), insects (Drosophila), and mammals including humans. Although the ligands may be different the downstream elements activated by this superfamily of receptors is highly conserved. Similarly, the FGFRs belong to a subclass of the RPTK superfamily and share many additional structural features including an acidic region between the first and second Ig loops and an intracellular split tyrosine-kinase domain" (see page 11, 1st full paragraph of the response filed December 4, 2006).

Contrary to Applicant's assertions, the inventions are patentably distinct for the reasons set forth in the Office action mailed October 5, 2006, and because they are so distinct, the search necessary to examine claims directed to any one of the inventions is not the same, nor is it coextensive with the search required to examine claims directed to any other. Notably, each different RPTK is a structurally and functionally distinct receptor; and contrary to Applicant's assertions it is appreciated by the artisan that the superfamily of receptor protein tyrosine kinases (RPTKs) is extraordinarily large and

highly diverse, both in structure and function, and which itself comprises a plurality of distinct families composed of various members that still differ substantially from one another. For example, as noted at page 7 of the Office action mailed October 5, 2006: "RON binds to macrophage stimulating protein (MSP) and has been implicated in the functional regulation of mononuclear phagocytes. On the other hand, IGF-1R binds to IGF, which leads to the subsequent activation of multiple signaling pathways such as Grb and PI-3K". To further elaborate on this point with particular respect to the FGF receptors, it is noted that FGF receptors 1, 2, 3 and 4 are also structurally and functionally distinct receptors, as each receptor has a different amino acid sequence and is functionally distinct from the others. As an example of such differences, FGFR1 binds with high affinity to the FGF2 ligand, while in contrast FGFR3 binds with low affinity to the FGF2 ligand. Moreover, very recently, members of this family have been recognized as having striking functional diversity because, for example, whereas, FGFR1 and FGFR4 have the ability to facilitate translocation of exogenous FGF-1 to the cytosol and nucleus, FGFR2 and FGFR3 completely lack this ability[1]. Consequently, it is apparent, given such structural and functional diversity among family members, that different searches must be performed to examine claims directed to each of the different groups of inventions; and a need to perform more than one search would constitute a serious burden.

Additionally, Applicant has argued that searching all the amino acid sequences directed to unique SEQ ID Nos of variable heavy chain CDR3 regions and variable light chain CDR3 regions "would not pose undue burden on the Patent and Trademark Office".

In response, contrary to Applicant's assertions, searching and examining amino acid sequences from more than one antibody would pose an undue burden on the Patent and Trademark Office. Notably, the disclosed antibodies comprise different CDR sequences and are disclosed as having different functional properties. Furthermore, as each antibody comprises CDRs with different amino acid sequences, different sequence

[1] See Sorensen et al. (*J. Cell Sci.* 2006 Oct 15; **119** (Pt 20): 4332-4341).

searches in up to 10 different databases are required to consider claims to each antibody which presents an undue burden on the Patent and Trademark Office due to the complex nature of the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the Examiner. Therefore, since different searches must be performed and different non-prior art issues must be considered in examining each structurally and functionally different antibody, considering amino acids sequences from more than one described antibody would constitute a serious burden.

Furthermore, Applicant has provided no evidence to establish why the remaining groups are sufficiently related or why the requirement for restriction is improper. Clearly different searches and issues are raised in the examination of each group, which would create a burden on the Office. See MPEP 808.02.

Therefore, for these reasons and the reasons set forth in the Office action mailed October 5, 2006, there would be a serious burden in examining the product and process claims together and the restriction/election requirement is deemed proper and therefore made FINAL

Information Disclosure Statement

7. The references cited in the information disclosure statements filed on December 15, 2003 and June 29, 2006 have been considered.

Priority

8. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of US provisional application 60/299,187 is acknowledged.

However, claims 1, 4-10, 15, 17, 22 and 31 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of PCT/IL02/00494, namely June 20, 2002.

Drawings

9. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: 9B, 9C, 16B, 16C, 16D and 16E. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

10. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is

permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is GelCode™ (see page 38).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

(b) The specification is objected to because the Brief Description of the Drawings fails to comply with 37 CFR 1.84(p)(5) which requires every reference character to be described in the brief description. In this case, the description of Figure 9 does not specifically refer to Figure 9B and 9C and the description of Figure 16 does not specifically refer to Figure 16B, 16C, 16D and 16E.

(c) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

11. Claims 4, 7 and 8 are objected to as being drawn in the alternative to the subject of non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1, 4-10, 15, 17, 22 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-10, 15, 17, 22 and 31 are indefinite for the following reasons:

(a) Claims 1, 4-10, 15, 17, 22 and 31 are indefinite because of the recitation of an "antibody which has *increased affinity* for a fibroblast growth factor receptor" [italics added for emphasis] in claim 1. Notably, the recitation renders the claims indefinite because it is cannot be ascertained what comparison is made in determining if an antibody has "*increased affinity* for a fibroblast growth factor receptor". The term "*increased affinity*" is a relative term that is not defined by the claim; and the disclosure does not provide a standard for ascertaining the requisite extent to which the affinity of the molecule is increased. Relative to what standard is the affinity of the molecule for a fibroblast growth factor necessarily increased? Without such information, the comparison being made to determine if an antibody has increased affinity is not determinable, for example. For these reasons, the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(b) Claim 1, 4-10, 15, 17, 22 and 31 are indefinite because of the use of the term "fibroblast growth factor receptor" in, for example, claim 1 or "FGFR3", in, for example, claim 4. The use of these terms to identify the protein for which the claimed antibody has increased affinity to which the claim is directed renders the claim indefinite because it fails to point out with the requisite particularity the identity of the protein. Different laboratories often use the same nomenclature to identify distinct proteins. In

this instance, the term "fibroblast growth factor receptor" is used in the relevant art to identify multiple different proteins, e.g., FGFR1, FGFR2, FGFR3 and FGFR4. Webster et al (TIG, 13(5):178-182, IDS filed 12/15/2003) teaches FGFR1, FGFR2, FGFR3 and FGFR4 are structurally and functionally distinct proteins, since, for example, each protein displays a distinct pattern of expression during development; see entire document (e.g., the page 178, left column). Furthermore, Webster et al teach that the term FGFR3 refers to at least 16 structurally and functionally distinct fibroblast growth factor receptors as 16 different single amino acid substitutions have been identified in FGFR3 that result in multiple different diseases. Notably, for example, Webster et al teach that FGFR3 with a Lys650Glu substitution causes a syndrome named Thanatophoric dysplasia type II, while FGFR3 with a Lys650Met substitution causes a distinct syndrome named Novel skeletal dyslplasia (e.g., page 179, Table 1). Accordingly, because it is unclear or cannot be ascertained to which of the different proteins termed "fibroblast growth factor receptor" in, for example, claim 1 or "FGFR3"" the antibody must have increased affinity for, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

It is suggested that this issue be remedied by amending claim 19 to recite a limitation requiring the "fibroblast growth factor receptor" or "FGFR3", to comprise a particular amino acid sequence, which is disclosed in the specification, as filed, because such a limitation would serve to unambiguously identify the protein to which the claim is directed.

(c) Claims 6-10 are indefinite because in the recitation that the "molecule blocks *constitutive* activation" (italicized for emphasis) in claim 6. The Online Medical Dicitonary, 10th Edition (http://cancerweb.ncl.ac.uk/cgi-bin/omd?constitutive, viewed 7/23/2007, see Exhibit A) defines *constitutive* as meaning: "constantly present, whether there is a demand or not" (© Copyright 1997-2007 - The Centre for Cancer Education). Therefore, it appears that a fibroblast growth factor receptor that is constitutively active

is a receptor that has been modified such that it is always active (i.e., *on*) and without need of being activated (i.e., *turned on*). As such, how does one block the activation of something that is always active? For these reasons, the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1, 4-6, 8-10, 15, 17, 22 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even

for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In the instant case, claims 1, 4-6, 8-10, 15, 17, 22 and 31 are drawn to a structurally and functionally diverse genus of "molecules comprising the antigen-binding portion of an isolated antibody which has increased affinity for a structurally and functionally diverse genus of fibroblast growth factor receptor 3 (FGFR3) polypeptides and which block activation of said FGFR3 polypeptides", which do not necessarily specifically bind and block the activation of any particular FGFR3 polypeptide and do not necessarily comprise the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95. Due to the indefinite nature of antibodies that have increased affinity for FGFR3, the claims are being interpreted as encompassing antibodies that specifically bind FGFR3. Furthermore, due to the indefinite nature of blocking the *constitutive* activation of an FGFR3 that is always active, the claims are interpreted are being drawn to antibodies that block the ligand-dependent activation of FGFR3.

However, as will be explained in further detail in the following paragraphs, the specification only adequately describes antibodies which specifically bind to the fibroblast growth factor receptor 3 polypeptide comprising SEQ ID NO:1, wherein the antibody comprises the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 and blocks the ligand-dependent activation of said fibroblast growth factor receptor 3 polypeptide (see pages 51 and 7 that disclose the FGFR3 antibody comprising the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 which binds to and inhibits the ligand-dependent proliferation of cells expressing the fibroblast growth factor receptor 3 polypeptide).

Notably, the specification discloses at page 13 that FGF receptors include alternative splicing variants of the FGF receptors. Furthermore, at page 6 the specification discloses that multiple mutations are known to occur in FGFR3 that result in a receptor that is constitutively active.

In this case, the specification does not describe with any particularity the identifying structural and/or functional features of the genus of "fibroblast growth factor receptor 3 (FGFR3) polypeptides" encompassed by any splice variant or any

substitution in FGFR3 that causes constitutive activation. Notably, the specification, does not describe the structure of a sufficient number of species of the genus of "FGFR3 polypeptides", to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. Notably, while the specification provides evidence that the antibody comprising the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 binds to cells expressing the fibroblast growth factor receptor 3 polypeptide and inhibits the proliferation of these cells caused by the ligand-dependent activation of the expressed receptor, it does not describe any antibodies that block the ligand-dependent activation of any FGFR3 polypeptides that have mutations which cause constitutive activity in the FGFR3 polypeptide and does not describe how the particularly described fibroblast growth factor receptor 3 polypeptide comprising SEQ ID NO:1 is representative of the genus of "FGFR3 polypeptides" encompassed in this structurally and functionally diverse genus.

For example, it is established in the art that there is a high degree of unpredictability in assigning particular structures or functions to a protein based on sequence homology alone because a protein's structure is dependent on its given amino acid sequence and cannot be determined *a priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure. To illustrate this, Skolnick et al. (*Trends in Biotechnology*, **18**: 34-39, 2000), discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Furthermore, as evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133, 3rd paragraph). Finally, Tosatto et al state, "the

link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Therefore, the structure and function of the genus of "FGFR3 polypeptides" is highly unpredictable and one of skill in the art would not immediately envision which polypeptides would have the requisite functions. Notably, since the genus of "FGFR3 polypeptides" is not adequately described the claimed antibodies are not adequately described.

To further support the assertion that the genus of "FGFR3 polypeptides" is not adequately described in the specification, it is noted that Webster et al (TIG, 13(5):178-182, 1997, IDS filed December 15, 2003) teach that mutations in FGFR3 occur in the extracellular domain, the transmembrane domain and the intracellular kinase domain resulting receptors that are active in the absence of ligand, i.e, these receptors display constitutive kinase activity. Therefore, one of skill in the art would not immediately envision which "FGFR3 polypetides" would have their activation blocked by the particularly described antibody and which would not. Finally, in this case there is factual evidence that different mutations in FGFR3 create structurally and functionally distinct polypeptides whose activation is not inhibited by a neutralizing antibody that inhibits the ligand-dependent activation of the FDFR3 polypeptide comprising SEQ ID NO:1. For example, Trudel et al (Blood, 107(10):4039-4046, 2006) teach an FGFR3 neutralizing antibody that inhibits the ligand-dependent activation of a wild-type FGFR3, but which does not inhibit the activation of an FGFR3 polypeptide with a K650E or a 807C substitution as these receptors are active in the presence of the antibody. Therefore, the FGFR3 polypeptide comprising SEQ ID NO:1 whose activation is blocked by the FGFR3 antibody comprising the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 would not be considered to be representative of the genus of "FGFR3 polypeptides" as one of skill in the art would not be able to immediately envision or recognize which FGFR3 polypeptide would have their activation blocked by a particular antibody.

Additionally, where the claims are drawn to molecules comprising only the

variable heavy chain CDR3 region of SEQ ID NO:24 and the variable light chain CDR3 region of SEQ ID NO:25, it is submitted that only describing only two out of the six CDR sequences of an antibody fails to adequately describe the antigen-binding portion of an antibody.

To elaborate on this point, Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition and teaches that a naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

In view of Mariuzza et al., it is apparent that having only described two of the six CDRs that form the antigen binding site of an antibody does not suffice to describe the particularly identifying structural feature of the antibody that correlates with the antibody's ability to bind to the antigen. Absent a description of the at least minimal structural features correlating with a functional ability to bind to a particular antigen, which are shared by members of a genus commonly sharing this function, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish members of the genus from other antibodies. For this reason, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Thus, the specification only adequately describes antibodies which specifically bind to the fibroblast growth factor receptor 3 polypeptide comprising SEQ ID NO:1, wherein the antibody comprises the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 and blocks the ligand-dependent activation of said fibroblast growth factor receptor 3 polypeptide. Furthermore, such an antibody is not representative of the genus of structurally and

functionally diverse antibodies encompassed by the claims as one of skill in the art would not recognize which FGFR3 polypeptides this antibody would have increased affinity for or that this antibody would block activation of FGFR3 polypeptides that were constitutively active.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Although the skilled artisan could potentially screen candidate antibodies comprising the heavy chain variable region CDR3 of SEQ ID NO: 24 and the light chain variable region CDR3 of SEQ ID NO: 25, for example, or alternatively a library of antibodies to identify those that are capable of blocking ligand-dependent activation of a FGFR3 polypeptide and comprise the requisite structural feature(s) (e.g., a heavy chain variable region CDR3 of SEQ ID NO: 24 and the light chain variable region CDR3 of SEQ ID NO: 25), it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of*

Rochester v. G.D. Searle Co., 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to a genus of structurally disparate antibodies that have increased affinity for a "FGFR3 polypeptide" and which block activation of said "FGFR3 polypeptide", an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

It is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of blocking activation of the FGFR3 polypeptide does not distinguish the antibodies, from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or

chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Given the lack of particularity with which the "molecules comprising the antigen-binding portion of an isolated antibody which has increased affinity for a structurally and functionally diverse genus of fibroblast growth factor receptor 3 (FGFR3) polypeptides and which block activation of said FGFR3 polypeptides", to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of "molecules comprising the antigen-binding portion of an isolated antibody which has increased affinity for a structurally and functionally diverse genus of fibroblast growth factor receptor 3 (FGFR3) polypeptides and which block activation of said FGFR3 polypeptides", to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Notably, claim 7 is herein interpreted as being drawn to a molecule comprising the antigen binding portion of an antibody that binds to the FGFR3 polypeptide comprising SEQ ID NO:1 and blocks activation of said FGFR3 polypeptide, wherein the molecule comprises the variable heavy chain region of SEQ ID NO:106 and the variable light chain region of SEQ ID NO:95. Although claim 1 is directed to a genus of "fibroblast growth factor receptors", as opposed to the FGFR3 polypeptide of SEQ ID NO: 1, it is evident from a reading of the specification that an antibody comprising a variable heavy chain region of SEQ ID NO:106 and a variable light chain region of SEQ ID NO:95 specifically binds to the FGFR3 polypeptide comprising SEQ ID NO:1, so as to block ligand-dependent activation of said FGFR3 polypeptide (see page 51 which discloses an FGFR3 antibody that binds to the wild-type FGFR3 polypeptide comprising SEQ ID NO:1 and page 7 that discloses that the antibody comprises the variable heavy chain region of SEQ ID NO:106 and the variable light chain region of SEQ ID NO:95. Therefore, claim 7 has not been included in this rejection.

16. Claims 1, 4-10, 15, 17, 22 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** antibodies that specifically bind to the fibroblast growth factor receptor 3 (FGFR3) polypeptide comprising SEQ ID NO:1, wherein the antibody comprises the 6 CDRs from the variable heavy chain region of SEQ ID NO:106 and the variable light chain region of SEQ ID NO:95 and blocks the ligand-dependent activation of said FGFR3 polypeptide, and **while being enabling for making and using** antibodies encompassed by the claims, which are taught by the prior art, **does not reasonably provide enablement for making and using** all molecules encompassed by the full scope of the claims, for example, antibodies that specifically bind the constitutively active fibroblast growth factor receptor 3 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 but for the substitution of glycine at position 380 by arginine, wherein the antibody comprises the variable heavy chain region of SEQ ID NO:106 and the variable light chain region of SEQ ID NO:95, so as to block the ligand-dependent activation of said FGFR3 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims, as failing to comply with the written description requirement, the claims are drawn to molecules comprising antigen binding portions of an isolated antibody which has increased affinity for any fibroblast growth factor receptor 3 and which blocks activation of said fibroblast growth factor receptor 3 and such molecules that do not necessarily contain six CDRs of an antibody.

However, the specification only teaches one of skill in the art how to make and use antibodies that have six CDRs that specifically bind and block the ligand-dependent activation block of a fibroblast growth factor receptor 3 polypeptide comprising SEQ ID NO:1 (see page 51).

Notably, the specification does not provide any specific non-general guidance that would allow one of skill in the art to make antibodies that block the constitutive activation of FGFR3 polypeptides with mutations that result in receptors with constitutive kinase activity, such as the fibroblast growth factor receptor 3 polypeptide with a Glycine 380 to Arginine substitution and therefore one of skill in the art would be subject to undue experimentation to make, e.g., antibodies comprising the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95 that would specifically bind the fibroblast growth factor receptor 3

polypeptide with a Glycine 380 to Arginine substitution and block its activation. Additionally, the specification does not provide any specific non-general guidance that would allow one of skill in the art to make antibodies comprising less than the 6 CDRs of a parent antibody that would be expected to retain the antigen binding function of the parent antibody. Finally, the specification does not provide any specific non-general guidance that would allow one of skill in the art.

Notably, as evidenced by Scklonick et al, Tosatto et al and Jones (supra) predicting the function of a polypeptide given its amino acid sequence is highly unpredictable, so one of skill in the art would be subject to undue experimentation to identify other FGFR3 polypeptides whose activation could be inhibited with the claimed antibodies.

Furthermore, it is noted that the specification teaches that a Glycine 380 to Arginine substitution in the FGFR3 polypeptide comprising SEQ ID NO:1 results in a FGFR3 receptor that is constitutively active and consequently is active in the absence of any ligand. Therefore, it is apparent that the FGFR3 polypeptide can be activated by mutations as well as by ligands, yet the specification fails to teach how to make antibodies that block the activation of FGFR3 receptors caused by mutations as the specification does not teach any antibodies that block mutations in the FGFR3 polypeptide that result in constitutive kinase activity. Thus, as the specification does not provide any specific guidance on how to make antibodies that block the constitutive activation of any FGFR3 polypeptide, one of skill in the art would be subject to undue experimentation to make such antibodies. Finally, while claim 15 is drawn to antibodies that bind to and block the ligand-dependent activation of the FGFR3 polypeptide, it is noted for the same reasons and because Webster et al (supra), Trudel et al (supra) and the specification teach multiple FGFR3 polypeptides that are constitutively active that no longer require ligand-dependent activation, one of skill in the art would be subject to undue experimentation to block the ligand-dependent activation of FGFR3 polypeptides that are constitutively active.

Additionally, the claims encompass antigen-binding portions from isolated antibodies containing less than 6 CDRs from a parent antibody. It is well established in

the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; 84 (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). As further evidenced by Rudikoff et al (Proceedings National Academy Sciences. USA 1982 Vol. 79: page 1979), the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. As evidenced by these teachings, even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. It is unlikely that antibodies that do not contain all of 6 CDRs from the FGFR3 antibody comprising the variable heavy chain amino acid sequence of SEQ ID: 106 and the variable light chain amino acid sequence of SEQ ID NO:95, would have the required binding function. Therefore, the specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies comprising fewer than all six CDRs that retains binding of the parent antibody and one of skill in the art would be subject to undue experimentation to produce such an antibody.

Notably, the specification does not provide sufficient guidance or direction as to

how to produce such an antibody comprising only heavy and light chain CDR3 regions from the disclosed FGFR3 antibody that retains binding of the parent antibody and there is no working example of such an antibody.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other antibodies that block the activation of any fibroblast growth factor receptor 3 polypeptide and antibodies comprising SEQ ID NO:24 and SEQ ID NO:25 with this function that are encompassed by the claims; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

With regard to claim 7, as discussed in the written description rejection above, the specification teaches an antibody comprising a variable heavy chain region of SEQ ID NO:106 and a variable light chain region of SEQ ID NO:95 specifically binds to the FGFR3 polypeptide comprising SEQ ID NO:1, so as to block ligand-dependent activation of said FGFR3 polypeptide (see, for example, page 51). Nonetheless, there is no evidence, nor would it be expected that such an antibody binds any other member of the genus of "fibroblast growth factor receptors" to which claim 7 is directed, or that such an antibody might block activation of any other "fibroblast growth factor receptor". Therefore, while the specification would reasonably enable the skilled artisan to make and use an antibody comprising a variable heavy chain region of SEQ ID NO:106 and a

variable light chain region of SEQ ID NO:95 specifically binds to the FGFR3 polypeptide comprising SEQ ID NO:1, so as to block ligand-dependent activation of said FGFR3 polypeptide, it would not enable the artisan to make and use such an antibody that is capable of binding any other "fibroblast growth factor receptors", so as to block its activation, without undue and/or unreasonable experimentation. It is for this reason that claim 7 has been included in this rejection.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 4-6, 10, 15, 17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Cappellen et al (WO 00/68424, 2000, IDS filed December 15, 2003).

The claims are herein drawn to antibodies that specifically bind a fibroblast growth factor receptor 3 polypeptide and block the ligand-dependent activation of said

fibroblast growth factor receptor 3 polypeptide and said antibody in compositions comprising a pharmaceutically acceptable carrier. Due to the indefinite nature of antibodies that have increased affinity for FGFR3, the claims are being interpreted as encompassing antibodies that specifically bind FGFR3; as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, it is not apparent, nor can it be ascertained to what, if any extent the affinity of the antibody is necessarily increased relative to any other antibody because the standard for comparison is not defined in the claim or in the disclosure. Furthermore, due to the indefinite nature of claim 6, reciting that the antibody blocks *constitutive* activation of an FGFR3 that is always active, claim 6 is herein interpreted are being drawn to antibodies that block the ligand-dependent activation of FGFR3.

Cappellen et al teach fibroblast growth factor receptor 3 polypeptides including splice variants FGFR3-IIIb and FGFR3-IIIc and constitutively activating mutations in FGFR3 comprising substitutions R248C and S249C (see entire document, e.g., page 1 and 2). Furthermore, Cappellen et al teach that inhibitors of FGFR3 include antibodies that specifically bind an FGFR3 polypeptide, and in particular inhibitors include antibodies that are specific for the extracellular region of the FGFR3-IIIb splice variant. Finally, Cappellen et al teach compositions comprising said antibodies, which are suitable for injection (e.g., page 4 and claim 19), and so would necessarily comprise a pharmaceutically acceptable carrier, such as water.

While, Cappellen et al do not expressly teach that these inhibitory antibodies block the ligand-dependent activation of FGFR3, the antibodies of Cappellen et al are structurally indistinguishable from the claimed antibodies and bind the same antigen as the instantly claimed invention. Therefore, absent a showing of any difference, the antibodies of Cappellen et al are deemed the same as the claimed invention. Notably, since the Patent and Trademark Office does not have the facilities for examining and comparing the inhibitory FGFR3 antibodies of Cappellen et al with that of the instant application, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA

197) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In summary, the FGFR3 antibodies and pharmaceutical compositions disclosed in the prior art are materially and structurally indistinguishable from the FGFR3 antibodies and pharmaceutical compositions. Therefore, absent a showing of any difference, the claimed FGFR3 antibodies and pharmaceutical compositions and FGFR3 antibodies and pharmaceutical compositions disclosed by the prior art are deemed the same.

19. Claims 1, 4-6, 10, 15, 17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnston et al (JBC, 270(51):30643-30650, 1995) as evidenced by Chellaiah et al (JBC, 274(49): 34785-34794, 1999).

The claims are herein drawn to antibodies that specifically bind a fibroblast growth factor receptor 3 polypeptide and block the ligand-dependent activation of said fibroblast growth factor receptor 3 polypeptide and said antibody in compositions comprising a pharmaceutically acceptable carrier. Due to the indefinite nature of antibodies that have increased affinity for FGFR3, the claims are being interpreted as encompassing antibodies that specifically bind FGFR3; as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, it is not apparent, nor can it be ascertained to what, if any extent the affinity of the antibody is necessarily increased relative to any other antibody because the standard for comparison is not defined in the claim or in the disclosure. Furthermore, due to the indefinite nature of claim 6, reciting that the antibody blocks *constitutive* activation of an FGFR3 that is always active, claim 6 is herein interpreted are being drawn to antibodies that block the ligand-dependent activation of FGFR3.

Johnston et al teach polyclonal FGFR3 antibodies that were raised against the Ig II extracellular domain of FGFR3 and specifically bind FGFR3 polypeptides that comprise this domain (see entire document, e.g., page 30644, right column, Figure 1 and Figure 2). As evidenced by Chellaiah et al, the Ig II extracellular domain of FGFR3 is required for FGF9 ligand binding specificity. Johnston et al further teach said FGFR3

antibodies in compositions for immunostaining of cells (e.g., Figure 3) that would inherently comprise a pharmaceutically acceptable carrier such as water.

While, Johnston et al do not expressly teach that these polyclonal antibodies block the ligand-dependent activation of FGFR3, the antibodies of Johnston et al are structurally indistinguishable from the claimed antibodies and bind to the same antigen as the instantly claimed invention. Moreover, as evidenced by Chellaiah et al, the antibodies of Johnston et al bind in a region of FGFR3 known to be important for ligand binding. Therefore, absent a showing of any difference, the antibodies of Johnston et al are deemed the same as the claimed invention. Notably, since the Patent and Trademark Office does not have the facilities for examining and comparing the FGFR3 antibodies of Johnston et al with that of the instant application, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In summary, the antibodies and compositions disclosed in the prior art are materially and structurally indistinguishable from the instantly claimed antibodies and compositions. Therefore, absent a showing of any difference, the claimed antibodies and compositions and the antibodies and compositions disclosed by the prior art are deemed the same.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 1 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable Cappellen et al (WO 00/68424, 2000, IDS filed December 15, 2003), in view of US Patent 5,843,450 (Dawson et al, 1998).

The claims are herein drawn to kits comprising an antibody which binds a fibroblast growth factor receptor 3 polypeptide, further comprising at least one reagent and instructions for use.

Cappellen et al teach what is set forth in the above 102 (b) rejection.

However, Cappellen et al not expressly FGFR3 antibodies comprised in kits with other reagents and instructions for use.

This deficiency is made up for in the teachings of Dawson et al. Dawson et al teach packaging primary antibodies for detecting polypeptides into kits comprising other

reagents and instructions for use (see entire document, e.g., column 22).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the FGFR3 antibodies taught by Cappellen et al into the kits of Dawson in order to make a kit to detect the FGFR3 polypeptide.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because primary antibodies where commonly placed into kits at the time the invention was made in order to provide convenience for detecting proteins as evidenced by Dawson et al and one of skill in the art would have a reasonable expectation of success in making such kits since all the components comprised in the kit were available.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

23. Claims 1 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable Johnston et al (JBC, 270(51):30643-30650, 1995), in view of US Patent 5,843,450 (Dawson et al, 1998).

The claims are herein drawn to kits comprising an antibody which binds a fibroblast growth factor receptor 3 polypeptide, further comprising at least one reagent and instructions for use.

Johnston et al teach what is set forth in the above 102 (b) rejection.

However, Johnston et al not expressly FGFR3 antibodies comprised in kits with other reagents and instructions for use.

This deficiency is made up for in the teachings of Dawson et al. Dawson et al teach packaging primary antibodies for detecting polypeptides into kits comprising other reagents and instructions for use (see entire document, e.g., column 22).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the FGFR3 antibodies taught by Johnston et al into the kits of Dawson in order to make a kit to detect the FGFR3 polypeptide.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because primary antibodies where commonly placed into kits at the time the invention was made in order to provide convenience for detecting proteins as evidenced by Dawson et al and one of skill in the art would have a reasonable expectation of success in making such kits since all the components comprised in the kit were available.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

24. No claims are allowed.

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Williams et al (US Patent, 5707,632, published 1998, IDS filed 12/15/2003) teach fibroblast growth factor receptor polypeptides and polyclonal antibodies that specifically bind said polypeptides.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

bd
July 23, 2007

constitutive

Constantly present, whether there is demand or not. Thus some enzymes are constitutively produced, whereas others are inducible.

(18 Nov 1997)

Previous: constitutional thrombopathy, constitutional ulcer, constitution and bylaws
Next: constitutive enzyme, constitutive gene, constitutive heterochromatin